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A short and efficient asymmetric synthesis of (−)-frontalin, (−)-*exo*-isobrevicomin and a volatile contributor of beer-aroma

Surendra Singh, Patrick J. Guiry *

Center for Synthesis and Chemical Biology, School of Chemistry and Chemical Biology, UCD Conway Institute, University College Dublin, Belfield, Dublin 4, Ireland

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ABSTRACT

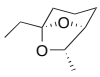
The natural products, (−)-frontalin and (+)-*exo*-isobrevicomin were synthesized employing Sharpless asymmetric epoxidation and $ZrCl_4$-catalyzed intramolecular acetalization as the key steps. (−)-Frontalin was synthesized in three steps with a 61.4% overall yield and 89.9% ee and (−)-*exo*-isobrevicomin also obtained in an overall satisfactory yield of 10.1% and 97% ee. We have also synthesized the volatile contributor of beer aroma in a 96% ee.

1. Introduction

Natural products with a 6,8-dioxabicyclo[3.2.l]octane skeleton have attracted much attention because of their intriguing biological activities; examples include the aggregation pheromones frontalin **1**, brevicomin **2**, and isobrevicomin **3**. (−)-Frontalin is known to be the aggregation pheromone of the southern pine beetle, *Dendroctunus frontalis*, isolated by Kinzer and co-workers[1] and (1*S*, 5*R*)-1,5-dimethyl-6,8-dioxabicyclo[3.2.1] octane is its biologically active form, whereas its enantiomer has been reported to be inactive.[2] (−)-*exo*-Isobrevicomin **3**, (1*S*, 5*R*, 7*S*)-5-ethyl-7-methyl-6,8-dioxabicyclo[3.2.1]octane, was isolated from the male mountain pine beetle, *Dendroctonus ponderosae* in 1996 by Francke and co-workers and its structure confirmed by synthesis starting from (+)-tartaric acid.[3]

1: Frontalin

2: *exo*-Brevicomin



3: *exo*-Isobrevicomin

During a study to develop new protection/deprotection methodologies of use in total synthesis, we have recently discovered a $ZrCl_4$-catalyzed formation of δ-lactones.[4] We subsequently exploited this in an asymmetric synthesis of both enantiomers of mosquito attractant pheromones.[5] We have also reported an extension of our investigations in this area in which we described a microwave-assisted, asymmetric synthesis of substituted tetrahydropyrans, which were useful synthons for an asymmetric synthesis of (+)-*exo*- and (+)-*endo*-brevicomin.[6] Herein, we wish to disclose a further extension of this synthetic methodology in a short and efficient synthesis of (−)-frontalin and (−)-*exo*-isobrevicomin.

Numerous asymmetric syntheses of frontalin **1** have been reported but the development of a short synthetic route with good overall yield was lacking and therefore of interest.[7] Our retro synthetic plan for the synthesis of (−)-1*S*, 5*R*-frontalin **1**, outlined in Scheme 1, proposed that the key quaternary carbon stereocentre in **4** was to be synthesized by the ring opening of (+)-epoxide **5** with the Grignard reagent derived from 2-(2-bromoethyl)-2-methyl-1,3-dioxolane (**6**).

Thus, (+)-epoxide **5** was synthesized in 87% yield, employing Sharpless asymmetric epoxidation using 10 mol % of $Ti(O^iPr)_4$ and 15 mol % of (−)-DIPT as the source of chirality and cumene hydroperoxide as oxidant at −20 °C for 36 h (Scheme 2). The ring opening of epoxide **5** was carried out at −78 °C in THF using a catalytic amount of CuI (10 mol %) with 3 equiv of the Grignard reagent derived from 2-(2-bromoethyl)-2-methyl-1,3-dioxolane (**6**). The diol **4** was treated with $ZrCl_4$ (10 mol %) in methanol under microwave irradiation (150 W) for 10 min to afford (−)-frontalin in an 86% yield and 89.9% ee. The enantiomeric excess was determined by GC using a chiral β-dex column and its absolute configuration was determined by comparison with literature optical rotations.[8] We were unable to determine the enantioselectivity of the epoxidation step but can infer it from the enantiomeric excess of **1** as our previous work in this area had not found any loss of stereochemistry in the final cyclization step.[5] The unnatural enantiomer (+)-1*R*, 5*S*-frontalin **1** was synthesized in 92.8% ee, using the same synthetic sequence starting with the enantiomer of epoxide **5**.

We were also keen to apply this synthetic sequence to the synthesis of (−)-*exo*-isobrevicomin **3**, isolated from the male mountain

* Corresponding author. E-mail address: patrick.guiry@ucd.ie (P.J. Guiry).

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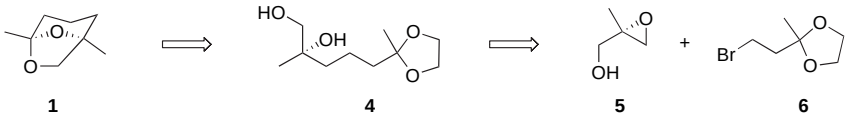
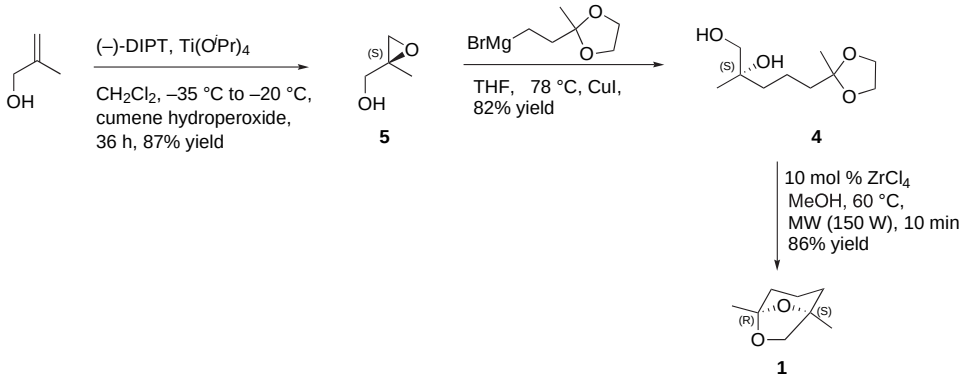


Scheme 1.



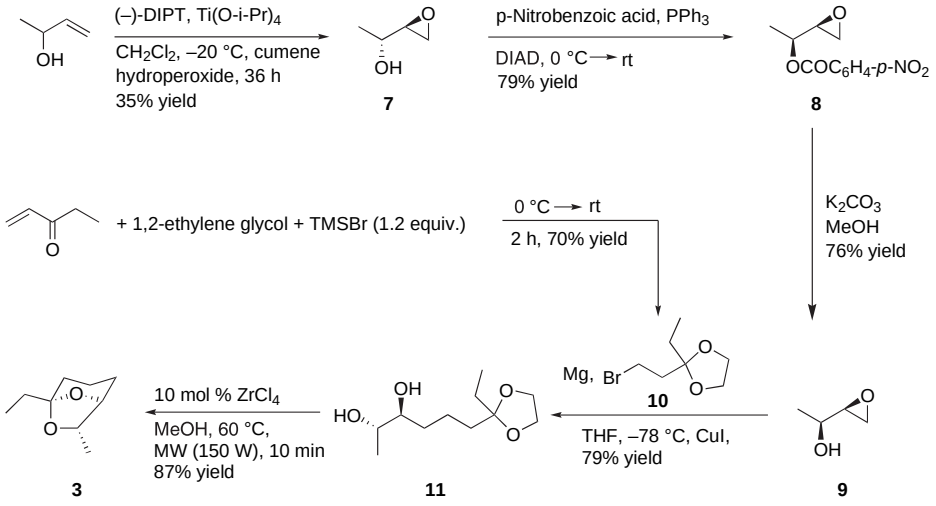
Scheme 2.

pine beetle, *Dendroctonus ponderosae*.[3] Unlike frontalin, there have been relatively few reported syntheses of (−)-*exo*-isobrevicomin.[9a–e] These include a low yielding (23.1%) chiral pool approach starting from (+)-tartaric acid,[9a] and catalytic asymmetric synthesis approaches using Sharpless asymmetric dihydroxylation of (*E*)-2-ethyl-2-(hex-4-enyl)-5,5-dimethyl-1,3-dioxane as the key step in a synthesis that proceeded in 3.57% overall yield[9b] and 99% ee and 5-ethyl-2-furfural followed by oxidative furan ring-expansion reaction to give **3** in 17% overall yield and 92.5% ee.[9c]

Our synthesis of (−)-*exo*-isobrevicomin commenced with the synthesis of epoxide **7** (35% yield) employing the Sharpless asymmetric epoxidation protocol[10a] at −20 °C for 36 h (Scheme 3). (2*S*, 3*R*)-1,2-Epoxy-3-butenol (**7**) was converted into its *p*-nitrobenzoate ester **8** in 79% yield using Mitsunobu reaction conditions.[10b] Hydrolysis of this benzoate ester **8** in methanol using K_2CO_3 afforded (2*S*, 3*S*)-1,2-epoxy-3-butenol (**9**) in 76% yield. The ring opening of epoxide **8** was performed at −78 °C using a catalytic amount of CuI (10 mol %) and the Grignard reagent derived from 2-(2-bromoethyl)-2-ethyl-1,3-dioxolane (**10**) at 50 °C in THF. 2-(2-Bromoethyl)-2-ethyl-1,3-dioxolane (**10**) was synthesized in a 70% yield from pent-1-en-3-one, 1.2 equiv of TMSBr and an excess of ethylene glycol. The intramolecular acetalization of *anti*-diol **11** was performed in methanol using a catalytic amount of $ZrCl_4$ under microwave irradiation to afford (−)-*exo*-isobrevicomin **3** in 87% yield and 97.9% ee. The enantiomeric excess[11] of (−)-*exo*-isobrevicomin was determined by GC using a chiral β-dex column and its absolute configuration was confirmed by comparison with literature optical rotations.[8]

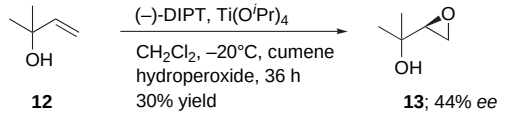
We have also explored this synthetic sequence for the synthesis of the (*S*)-enantiomer of 7,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane (**16**) which is known as a volatile contributor to the aroma of beer[12] and was first isolated from Japanese hop oil.[13] The asymmetric synthesis of beer aroma **15** has been accomplished using tartaric acid as the chiral starting material,[14a,b] through resolution,[14c] or via asymmetric cycloaddition employing Oppolzer's chiral sultam,[14d] Sharpless dihydroxylation[14e] and enantioconvergent biocatalytic hydrolysis of trisubstituted epoxides.[14f]

We also wished to investigate a synthetic sequence employing the ring opening of an enantioenriched epoxide, following by ring opening and subsequent $ZrCl_4$-catalyzed acetalization for the synthesis of beer aroma **16**. The Sharpless asymmetric epoxidation of 2-methylbut-3-en-2-ol in the presence of 10 mol % $Ti(O^iPr)_4$ and



Scheme 3.

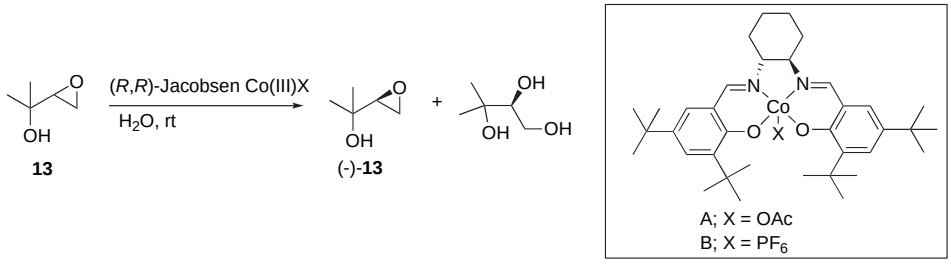
15 mol % L-(+)-DIPT and cumene hydroperoxide at −20 °C afforded epoxide **13** in 30% yield with poor enantioselectivity (44% ee), Scheme 4.



Scheme 4.

Racemic epoxide **13** was synthesized using a standard epoxidation procedure employing *m*-CPBA. Then we applied the hydrolytic kinetic resolution (HKR)[15] of racemic epoxide **13** in the presence of 1 mol % of (*R*, *R*)-Jacobsen Co(III)OAc and we obtained epoxide **13** (96% ee) in 30% isolated yield over 5 days (Table 1, entry 1).

Table 1
HKR of epoxide **13** using (*R*, *R*)-Jacobsen Co(III) salen



Entry[a]	Catalyst	Reaction time	Catalyst loading (mol %)	ee of epoxide **13**[b]	Isolated yield of epoxide **13**
1	A	5 days	1	96	30
2	B	15 h	0.5	79	40
3	B	8 h	1	99.9	25

[a] The Jacobsen Co(III)X (0.5–1 mol %) dissolved in the epoxide **13** and 0.5 equiv of water was added slowly at 0–5 °C and then the reaction mixture was stirred at a room temperature for the time mentioned.
[b] The enantiomeric excess of epoxide **13** was determined by Chiral GC using a β-dex column.

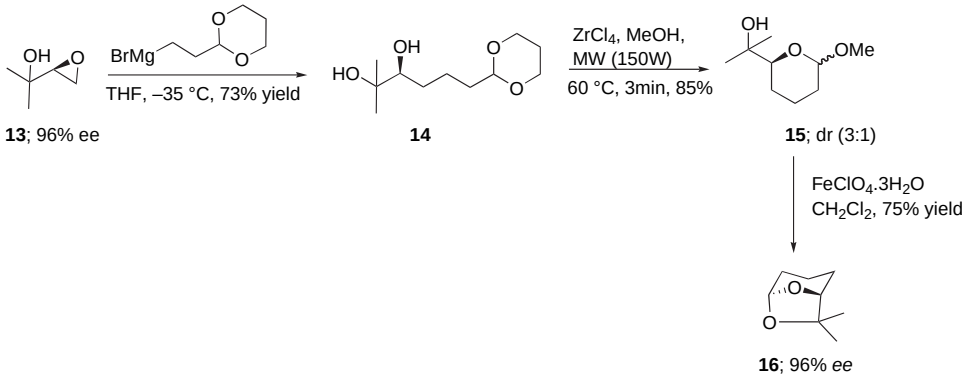
In addition, we altered the cobalt counterion from $^{-}$OAc to $^{-}$PF6, which we found to be more active in the HKR of racemic epoxide **13** leading to reaction completion in 8 h with 99.9% ee (Table 1, entry 3). In contrast, 0.5 mol % catalyst loading afforded epoxide **13** in 40% isolated yield and in 79% ee after 15 h (Table 1, entry 2). The enantioenriched (96% ee) epoxide **13** was converted to diol **14** in a 73% isolated yield using the Grignard reagent derived from 2-bromoethyl-1,3-dioxane in the presence of catalytic amounts of CuI (Scheme 5). The diol **14** was then treated with $ZrCl_4$ in methanol under microwave irradiation to give the 6-methoxytetrahydropyran **15** in 85% yield. The cyclization of compound **15** using $FeClO_4$ (0.2 equiv) in dichloromethane then afforded the volatile contributor of beer aroma **16** in 75% yield and 96% ee.

In summary we have developed a short and efficient synthesis of (−)-frontalin, the aggregation pheromone of the pine bark beetle in three steps with 61.4% overall yield and 89.9% ee. We have synthesized (−)-*exo*-isobrevicomin in six steps with 10.1% overall yield and 97.9% ee. We have also synthesized the volatile beer aroma in 96% ee. All syntheses had the Sharpless asymmetric epoxidation/HKR of racemic epoxide and our $ZrCl_4$-catalyzed bicyclic ring formation as the key steps.

2. Experimental

2.1. General remarks

2-Methylprop-2-en-1-ol, pent-1-en-3-one, but-3-en-2-ol, (+)-and (−)-diisopropyltartrate, Ti(O*i*-Pr)$_4$, 3-butene-2-one, TMSBr, $ZrCl_4$, anhydrous methanol, 1,2-ethylene glycol, *p*-nitrobenzoic acid, DIAD, CuI, and Mg turnings were obtained from commercial sources and were used as received. Proton and carbon nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR, respectively) were recorded on a 400 MHz Varian-Unity FT spectrometers (operating frequencies: ^{1}H, 400.13 MHz; ^{13}C, 100.61 MHz) at ambient temperature. In the case of ^{1}H and ^{13}C NMR spectra, the chemical shifts (δ) for all compounds are listed in parts per million downfield from tetramethylsilane using the NMR solvent as an internal reference. The reference values used for deuterated chloroform ($CDCl_3$) were 7.26 and 77.00 ppm for ^{1}H and ^{13}C NMR spectra, respectively. High resolution mass spectra were measured on a Waters/Micromass instrument. Optical rotation values were measured on a Perkin-Elmer polarimeter. GC analysis was done using a Schimadzu 2010



Scheme 5.

instrument using a chiral β-dex column. Thin layer chromatography was carried out using Merck Kieselgel 60 F_{254} silica gel plates. Column chromatography separations were performed using Merck Kieselgel 60 (Art. 7734). Solvents were dried immediately before use by distillation from standard drying agents. Molecular sieves (4 Å) were activated by heating overnight in an oven at 120 °C.

2.2. Experimental procedures and spectroscopic data for all compounds

*2.2.1. Synthesis of epoxide **5**.* A mixture of crushed 4 Å activated molecular sieves (1.0 g) and CH_2Cl_2 (30 mL) was cooled to −35 °C, titanium tetraisopropoxide (0.71 mL, 3 mmol) and (*R*, *R*)-(−)-DIPT (0.96 mL, 4.5 mmol) were added by syringe. After the mixture was stirred at −35 °C for 30 min, 2-methyl-prop-2-en-1-ol (2.34 g, 30 mmol) was added by addition funnel, followed by cumene hydroperoxide (6.98 mL, 45 mmol). The reaction mixture was stirred at −35 °C for 1 h and then stirred at −20 °C for 35 h. Aqueous saturated Na_2SO_4 (3 mL) was added and the mixture was diluted with Et_2O (30 mL). After the mixture was stirred at ambient temperature for 3 h, the resulting slurry was filtered through a pad of Celite, and the resulting yellow solution was concentrated. Excess cumene alcohol and cumene hydroperoxide were removed by silica gel chromatography (pentane/EtOAc, 4:1 then 100% Et_2O). Kugelrohr distillation (120 °C, 5 mbar) provided **5** as a colorless oil (2.30 g 87%).[7d] $[\alpha]_D^{20}$ +9.1 (*c* 2.05, $CHCl_3$) [lit.[7d] $[\alpha]_D^{25}$ +10.7 (*c* 2.0, $CHCl_3$)]; R_f (pentane/EtOAc, 4:1)=0.57; δ_H ^{1}H NMR (400 MHz, $CDCl_3$) 3.71 (1H, dd, *J* 12.3, 4.6 Hz, HO−C*H*$_2$), 3.59 (1H, dd, *J* 12.3, 8.4 Hz, HO−C*H*$_2$), 2.90 (1H, d, *J* 4.8 Hz, O−C*H*$_2$), 2.64 (1H, d, *J* 4.8 Hz, O−C*H*$_2$), 1.99 (1H, dd, *J* 8.4, 4.6 Hz, −OH), 1.35 (3H, s, Me); δ_C ^{13}C NMR (101 MHz, $CDCl_3$) 64.2, 57.2, 51.0, 18.0 ppm. GC−HRMS (EI), found 88.0521 $[M]^+$, $C_4H_{18}O_2$ requires 88.0524.

*2.2.2. (S)-2-Methyl-5-(2-methyl-1,3-dioxolan-2-yl)pentane-1,2-diol (**4**).* The Grignard derivative of 2-methyl-(2-bromoethyl)-1,3-dioxane was prepared by slow addition of the bromide (3.14 mL, 15 mmol) to preactivated magnesium turnings (3.60 g, 15 mmol) in THF (15 mL) with 1,3-dibromoethane as initiator (30 μL, 0.33 mmol) at 50 °C and then stirred for 45 min. The solution was then transferred to a two-necked flask containing copper (I) iodide (0.5 mmol) at −78 °C and stirred for 5 min. The epoxide (440 mg, 5 mmol) in THF (5 mL) was added dropwise over 20 min and stirring was continued for a further 1 h at −78 °C. Solid ammonium chloride (0.60 g) was added and the solution was stirred at room temperature for 10 min after which time a saturated ammonium chloride solution (15 mL) was added. The solution was extracted with ethyl acetate (6×40 mL) and the combined organic layers were washed with water (30 mL), brine (30 mL), and dried over magnesium sulfate. After removal of the solvent in vacuo the residue was purified by column chromatography using silica gel (pentane/EtOAc=4:1 →1:1 and then ethyl acetate). The compound **4** isolated as a pale yellow oil (856 mg, 82%).[7t] $[\alpha]_D^{20}$ −1.8 (*c* 1.40, $CHCl_3$) [lit.[7t] $[\alpha]_D^{20}$ −2.1 (*c* 1.0, Et_2O)]; R_f (pentane/EtOAc, 1:1)=0.48; δ_H ^{1}H NMR (400 MHz, $CDCl_3$) 4.04−3.84 (4H, m, −OC*H*$_2$−C*H*$_2$−O), 3.46 (H, d, *J* 10.9 Hz, HO−C*H*$_2$), 3.39 (H, d, *J* 10.9 Hz, HO−C*H*$_2$)1.67−1.62 (2H, m, −C−C*H*$_2$−CH$_2$), 1.56−1.39 (4H, m, CH$_2$−C*H*$_2$−C*H*$_2$−C), 1.31 (3H, s, anomeric-C*H*$_3$), 1.16 (3H, s, −OH−C(CH$_2$)−C*H*$_3$); δ_C (101 MHz, $CDCl_3$) 110.0, 72.8, 69.7, 64.6, 64.5, 39.5, 38.6, 23.7, 23.2, 18.3; HRMS (ESI), found 227.1387 $[M+Na]^+$, $C_{10}H_{20}O_4Na$ requires 227.1259.

*2.2.2.1. (R)-2-Methyl-5-(2-methyl-1,3-dioxolan-2-yl)pentane-1,2-diol (**4**).* All physical data are identical to (*S*)-**4** apart from $[\alpha]_D^{20}$ +1.8 (*c* 1.30, $CHCl_3$).

*2.2.3. Synthesis of (1S, 5R)-1,5-dimethyl-6,8-dioxa-bicyclo[3.2.1]octane (**1**).* $ZrCl_4$ (55 mg, 10 mol%) and diol **4** (480 mg, 2.35 mmol) were dissolved in methanol (1.5 mL) and irradiated under MW (150 W) at 60 °C for 10 min. The compound was purified by flash column chromatography using pentane/Et_2O (9:1) as the eluent but as **1** was volatile, so the solvent was evaporated by rotavapor at 40 °C and the remaining solvent was removed at 40 °C at 150 mbar vaccum, to give (−)-frontalin **1** as a colorless oil (287 mg, 86% yield).[7t] $[\alpha]_D^{20}$ −53.6 (*c* 1.44, 89.9% ee, Et_2O) [lit.[7h] $[\alpha]_D^{19}$ −53.7 (*c* 0.67, Et_2O), lit.[7j] $[\alpha]_D^{24}$ −50.3 (*c* 1.63, 89.1% ee, Et_2O), and lit.[7t] $[\alpha]_D$ −51.6 (*c* 0.5, 85% ee, Et_2O)]; R_f (pentane/Ether, 9:1)=0.75; δ_H ^{1}H NMR (400 MHz, $CDCl_3$) 3.90 (1H, d, *J* 6.7 Hz, −OC*H*$_2$−), 3.44 (1H, dd, *J* 6.7, 1.5 Hz, −OC*H*$_2$−), 1.94−1.79 (1H, m, −CH$_2$−C*H*$_2$−CH$_2$), 1.69−1.48 (5H, m, −C*H*$_2$−C*H*$_2$−C*H*$_2$), 1.42 (3H, s, O−C−C*H*$_3$), 1.31 (3H, s, O−C−C*H*$_3$); δ_C ^{13}C NMR (101 MHz, $CDCl_3$) 108.0, 80.0, 74.2, 34.5, 33.9, 24.7, 23.0, 18.0 ppm; GC−HRMS (EI), found 142.0994 $[M]^+$, $C_8H_{14}O_2$ requires 142.0994.

*2.2.3.1. (1R,5S)-1,5-Dimethyl-6,8-dioxa-bicyclo[3.2.1]octane (**1**).* All physical data are identical to (1*S*, 5*R*)-**1** apart from $[\alpha]_D^{20}$ +52.3 (*c* 1.05, 92.8% ee, Et_2O) [lit.[7e] $[\alpha]_D^{20}$ +54.3 (*c* 0.3, Et_2O), lit.[7c] $[\alpha]_D^{21}$ +52.4 (*c* 4.0, Et_2O)].

*2.2.4. Synthesis of epoxide **7**.* A mixture of crushed activated 4 Å molecular sieves (2.0 g) and CH_2Cl_2 (80 mL) was cooled to −35 °C, and titanium tetraisopropoxide (5.92 mL, 20 mmol) and (*R*, *R*)-(−)-DIPT (6.30 mL, 30 mmol) were added by syringe. After the mixture was stirred at −35 °C for 30 min, but-3-en-2-ol (6.9 mL, 80 mmol) was added by addition funnel, followed by cumene hydroperoxide (8.3 mL, 56 mmol). The reaction mixture was stirred at −35 °C for 1 h and then stirred at −20 °C for 35 h. The reaction work up and purification were performed identical to the synthesis of epoxide **7**.[10a] Kugelrohr distillation (120 °C, 5 mbar) provided **7** as a colorless oil (2.47 g, 35%). $[\alpha]_D^{20}$ −47.5 (*c* 1.1, $CHCl_3$) [lit.[7] $[\alpha]_D^{26}$ −16.9 (*c* 1.16, MeOH)]; R_f (pentane/EtOAc, 4:1)=0.42; δ_H ^{1}H NMR (400 MHz, $CDCl_3$) 3.99−3.91 (1H, m,CH$_3$−C*H*−OH), 2.98 (1H, dt, *J* 4.0, 3.2 Hz, O−C*H*$_2$−), 2.79−2.74 (1H, m, O−C*H*$_2$−), 2.71 (1H, dd, *J* 5.2, 4.0 Hz, O−C*H*$_2$−), 2.11 (1H, br s, −O*H*), 1.23 (3H, d, *J* 6.4 Hz, −CH−C*H*$_3$); δ_C ^{13}C NMR (101 MHz, $CDCl_3$) 64.7, 55.3, 43.4, 18.6 ppm. GC−HRMS (EI), found 88.0526 $[M]^+$, $C_4H_8O_2$ requires 88.0524.

*2.2.5. Synthesis of (R)-1-((R)-oxiran-2-yl)allyl 4-nitrobenzoate (**8**).* PPh_3 (752 mg, 4.5 mmol) and *p*-nitrobenzoic acid (1.180 g, 4.5 mmol) were dissolved in THF (6 mL) and DIAD (826 μL, 4.2 mmol) was added dropwise at 0 °C.[10b] Then the epoxide **7** (264 mg, 3 mmol) in THF (2 mL) was added slowly and stirred for 5 min at 0 °C and then warmed to room temperature. The reaction mixture was stirred for 55 min at room temperature and the majority of solvent was removed under reduced pressure. The residue was purified by column chromatography using pentane/EtOAc (9:1) as the eluent. Compound **8** (565 mg, 79% yield) was isolated as a light yellow solid, mp 51 °C; $[\alpha]_D^{20}$ +41.0 (*c* 1.42, $CHCl_3$); R_f (pentane/EtOAc, 9:1)=0.65; ν_{max} (KBr) 3115, 2997, 1729, 1273, 1103 cm^{-1} δ_H ^{1}H NMR (400 MHz, $CDCl_3$) 8.26 (4H, td, *J* 9.0, 6.8 Hz, O−CO-*p*-NO$_2$−C$_6$H$_4$−), 5.03 (1H, p, *J* 6.4 Hz, CH$_3$−C*H*−CH−), 3.26 (1H, ddd, *J* 6.4, 4.0, 2.4 Hz, O−C*H*−CH$_2$−), 3.00−2.85 (1H, m, −O−C*H*$_2$−), 2.73 (1H, dd, *J* 4.8, 2.4 Hz, −O−C*H*$_2$−), 1.49 (3H, d, *J* 6.4 Hz, −CH−C*H*$_3$); δ_C ^{13}C NMR (101 MHz, $CDCl_3$) 163.8, 150.6, 135.5, 130.8, 123.5, 73.0, 53.4, 44.6, 16.5 ppm; GC−HRMS (EI), found 194.0457 $[M-C_2H_4O]^+$, $C_9H_8NO_4$ requires 194.0448.

*2.2.6. Synthesis of (1R, 2R)-1,2-epoxy-ethanol (**9**).* The *p*-nitrobenzoate **8** (500 mg, 2.1 mmol) and K_2CO_3 (700 mg) were added to methanol (4 mL) at 0 °C and stirred for 5 min.[10b] The reaction mixture was sonicated for 1 min and then filtered through a pad of silica gel and washed with diethyl ether (30 mL). The solvent was removed under reduced pressure and the residue was purified by column chromatography using pentane/Et_2O (1:1) to give (1*R*, 2*R*)-1,2-epoxy-ethanol (**9**) as a liquid (140 mg, 76% yield). $[\alpha]_D^{20}$ +19.3 (*c* 1.0, $CHCl_3$); R_f (pentane/EtOAc, 4:1)=0.42; ν_{max} (liquid film) 3420,

2935, 1043 cm^{-1}. δ_H ^1H NMR (400 MHz, $CDCl_3$) 3.62–3.51 (m, 1H, CH_3–C*H*–OH), 2.95–2.91 (m, 1H, C*H*–CH_2–O), 2.79 (1H, t, *J* 4.5 Hz, CH–C*H*$_2$–O), 2.66 (1H, dd, *J* 4.5, 2.8 Hz, CH–C*H*$_2$–O), 2.55 (1H, br s, –OH), 1.27 (4H, d, *J* 6.5 Hz, CH–C*H*$_3$); δ_C ^{13}C NMR (101 MHz, $CDCl_3$) 68.1, 56.3, 45.1, 19.6 ppm; GC–HRMS (EI), found 88.0526 $[M]^+$, $C_4H_8O_2$ requires 88.0524.

*2.2.6.1. (1S, 2S)-1,2-Epoxy-ethanol (**9**).* All physical data are identical to (1*R*, 2*R*)-**9** apart from $[\alpha]_D^{20}$ −19.2 (*c* 0.85, $CHCl_3$).

*2.2.7. Synthesis of 2-(2-bromoethyl)-2-ethyl-1,3-dioxolane (**10**).* The mixture of pent-1-en-3-one (4.95 mL, 50 mmol) and ethylene glycol (11.2 mL, 200 mmol) were cooled to 0–5 °C and then TMSBr (7.92 mL, 60 mmol) added slowly under an inert atmosphere. The resulting mixture was stirred for 2 h at room temperature. The conversion of crude mixture was checked by ^1H NMR spectroscopy. The reaction mixture was then poured into a biphasic mixture of pentane (100 mL) and 5% sodium carbonate (50 mL) and the resulting mixture was stirred for 5 min. The organic layer was removed, then washed with 5% sodium thiosulfate (50 mL) and water (50 mL), and dried over anhydrous K_2CO_3. After removal of the solvent in vacuo, the residue was purified by vacuum distillation (85 °C, 4 mbar vacuum) to give the title compound **10** (7.31 g, 70% yield) as an oil. δ_H ^1H NMR (400 MHz, $CDCl_3$) 3.98–3.92 (4H, m, O–C*H*$_2$–C*H*$_2$–O), 3.46–3.32 (1H, m, CH_2–C*H*$_2$Br), 2.40–2.13 (m, 1H, C*H*$_2$–CH_2Br), 1.63 (2H, q, *J* 7.5 Hz, C*H*$_2$–CH_3), 0.92 (3H, t, *J* 7.5 Hz, CH_2–C*H*$_3$); δ_C ^{13}C NMR (101 MHz, $CDCl_3$) 111.1, 65.1 (2C), 40.6, 30.2, 27.0, 7.9.

*2.2.8. Synthesis of (2S, 3S)-6-(2-ethyl-1,3-dioxolan-2-yl)hexane-2,3-diol (**11**).* The Grignard derivative of 2-ethyl-(2-bromoethyl)-1,3-dioxane (**10**) were prepared by slow addition of the bromide **10** (936 mg, 4.5 mmol) to preactivated magnesium turnings (109 mg, 4.5 mmol) in THF (5 mL) and 1,3-dibromoethane as a initiator (9 μL, 0.1 mmol) at 50 °C and then stirred for 45 min. The solution was then transferred to a two-necked flask containing copper (I) iodide (0.15 mmol) at −78 °C and stirred for 5 min. The epoxide (1*R*, 2*R*)-**9** (132 mg, 1.5 mmol) in THF (1.5 mL) was added dropwise over 20 min and stirring was continued for a further 1 h at −78 °C. Solid ammonium chloride (200 mg) was added and the solution was stirred at room temperature for 10 min after which time a saturated ammonium chloride solution (5 mL) was added. The solution was extracted with ethyl acetate (6×20 mL) and the combined organic layers were washed with water (10 mL), brine (10 mL), and dried over magnesium sulfate. After removal of the solvent in vacuo the residue was purified by column chromatography using silica gel (pentane/ethyl acetate=4:1→1:1→0:1) to give compound **11** (250 mg, 79%) as a pale yellow oil, $[\alpha]_D^{20}$ −12.6 (*c* 1.0, $CHCl_3$); R_f (pentane/EtOAc, 1:1)=0.40; ν_{max} (liquid film) 3450, 2943, 1225, 1065 cm^{-1} δ_H ^1H NMR (400 MHz, $CDCl_3$) 3.92–3.86 (4H, m, O–C*H*$_2$–C*H*$_2$–O), 3.57–3.46 (1H, m, HO–C*H*–CH_3), 3.30–3.22 (1H, m, HO–C*H*–CH_2), 1.58 (2H, q, *J* 7.4 Hz, C*H*$_2$–CH_3), 1.49–1.28 (m, 6H, C*H*$_2$–C*H*$_2$–C*H*$_2$), 1.12 (3H, d, *J* 6.3 Hz, HO–CH–C*H*$_3$), 0.85 (3H, t, *J* 7.4 Hz, CH_2–C*H*$_3$); δ_C ^{13}C NMR (101 MHz, $CDCl_3$) 112.0, 75.9, 70.7, 64.9 (2C), 36.4, 33.3, 29.8, 19.7, 19.4, 8.1 ppm. HRMS (ESI), found 241.1410 $[M+H]^+$, $C_{11}H_{22}O_2Na$ requires 241.1416.

*2.2.8.1. (2R, 3R)-6-(2-Ethyl-1,3-dioxolan-2-yl)hexane-2,3-diol (**11**).* All physical data are identical to (2*S*, 3*S*)-**11** apart from $[\alpha]_D^{20}$ +12.8 (*c* 0.8, $CHCl_3$).

*2.2.9. Synthesis of (1S, 5R, 7S)-5-ethyl-7-methyl-6,8-dioxa-bicyclo [3.2.1]octane (**3**).* $ZrCl_4$ (13.5 mg, 10 mol%) and (2*S*, 3*S*)-diol **11** (127 mg, 0.58 mmol) were dissolved in methanol (1 mL) and irradiated under MW (150 W) at 60 °C for 10 min. The compound was purified by flash column chromatography using pentane/Et_2O (9:1) as the eluent but as **3** was volatile, the solvent was evaporated by rotavapor at 40 °C and then the remaining solvent was removed at 40 °C at 150 mbar vacuum. (−)-*exo*-Isobrevicomin **3** (79 mg, 87% yield) was isolated as a colorless oil,[3,9c] $[\alpha]_D^{20}$ −56.4 (*c* 1.13, 97.9% ee, Et_2O) [lit.[9b] $[\alpha]_D^{22}$ −60.4 (*c* 1.16, $CHCl_3$), lit.[9c] $[\alpha]_D^{28}$ −55.9 (*c* 1.0, $CHCl_3$)]; R_f (pentane/Et_2O, 9:1)=0.85; δ_H ^1H NMR (400 MHz, $CDCl_3$) 4.21 (1H, q, *J* 6.2 Hz, O–C*H*–CH_3), 4.05 (1H, br s, O–C*H*-six membered ring), 1.97–1.46 (8H, m), 1.18 (3H, d, *J* 6.2 Hz, O–CH–C*H*$_3$), 0.95 (3H, t, *J* 7.5 Hz, $-CH_2-CH_3$); δ_C ^{13}C NMR (101 MHz, $CDCl_3$) 109.6, 79.9, 75.5, 33.5, 30.6, 28.1, 21.6, 17.1, 7.2 ppm; GC–HRMS (EI), found 156.1149 $[M]^+$, $C_9H_{16}O_2$ requires 156.1149.

*2.2.10. Synthesis of (1R, 5S, 7R)-5-ethyl-7-methyl-6,8-dioxa-bicyclo [3.2.1]octane (**3**).* All physical data are identical to (1*S*, 5*R*, 7*S*)-**3** apart from $[\alpha]_D^{20}$ +52.3 (*c* 1.74, 97.0% ee, $CHCl_3$).

*2.2.11. Hydrolytic kinetic resolution of racemic 2-(oxiran-2-yl) propan-2-ol (**13**).* The Jacobsen catalysts (1*R*, 2*R*)-Co(III)OAc and (1*R*, 2*R*)-Co(III)PF_6 were prepared according to literature procedures.[15,16] (1*R*, 2*R*)-Co(III)OAc and PF_6 (0.5–1 mol%) were dissolved in the epoxide **13** and 0.5 equiv of water was added slowly at 0–5 °C and then the reaction mixture was stirred at a room temperature for appropriate time (see Table 1). The desired epoxide (*S*)-**13** was purified by column chromatography using pentane/ether (3:2) and R_f (pentane/EtOAc, 3:2)=0.20. The enantiomeric excess of (*S*)-**13** was determined by GC using a β-Dex chiral column.

*2.2.12. Synthesis of (S)-6-(1,3-dioxan-2-yl)-2-methylhexane-2,3-diol (**14**).* Compound **14** was synthesized in 73% yield using the same procedure as given above for compound **11**. $[\alpha]_D^{20}$ −22.5 (*c* 1.0, $CHCl_3$); R_f (pentane/EtOAc, 1:1)=0.40; ν_{max} (liquid film) 3422, 2945, 1220, 1061 cm^{-1}; δ_H ^1H NMR (400 MHz, $CDCl_3$) 4.54 (1H, t, *J* 4.1 Hz, –O–C*H*–CH_2–), 4.15–4.04 (m, 2H, –O–C*Hab*–CH_2), 3.83–3.69 (m, 2H, –O–C*Hab*–CH_2), 3.37 (1H, d, *J* 10.1 Hz, –CH_2–C*H*OH), 2.21–1.98 (2H, m,), 1.67 (3H, m,), 1.55–1.29 (4H, m), 1.19 (3H, s, –C*H*$_3$), 1.14 (3H, s, –C*H*$_3$); δ_C ^{13}C NMR (101 MHz, $CDCl_3$) 102.2, 78.3, 73.0, 66.9 (2C), 34.8, 31.3, 26.4, 25.8, 23.1, 21.1; HRMS (ESI), found 241.1412 $[M+Na]^+$, $C_{11}H_{22}O_4Na$ requires 241.1416.

*2.2.12.1. (S)-2-(6-Methoxy-tetrahydro-2H-pyran-2-yl)propan-2-ol (**15**).* $ZrCl_4$ (23 mg, 10 mol%) and diol **14** (218 mg, 1 mmol) were dissolved in methanol (1 mL) and irradiated under MW (150 W) at 60 °C for 3 min. The compound was purified by flash column chromatography using pentane/Et_2O (4:1). The compound **15** was isolated as a colorless liquid in 85% yield and a diastereomeric ratio of 3:1. R_f (pentane/Et_2O, 4:1)=0.25; ν_{max} (liquid film) 3450, 2950, 1034 cm^{-1}; δ_H ^1H NMR (400 MHz, $CDCl_3$) 4.74 (1H, d, *J* 3.0 Hz, –OC*H*–OMe (major diastereomer)), 4.32 (0.33H, dd, *J* 9.5, 2.1 Hz, –OC*H*–OMe (minor diastereomer)), 3.50 (1H, dd, *J* 11.7, 1.9, –C*H*–O–CH–OMe (major diastereomer)), 3.47 (s, 1H, –OMe, (minor diastereomer)), 3.33 (s, 3H, –OMe (major diastereomer)), 3.19 (0.33H, dd, *J* 11.4, 1.9 Hz, –C*H*–O–CH–OMe (minor diastereomer)), 1.22–1.94 (9H, m, both diastereomers), 1.20 (1H, s, HO–CC*H*$_3$ (minor diastereomer)), 1.18 (s, 3H, HO–CC*H*$_3$ (major diastereomer)), 1.16 (1H, s, (minor diastereomer)), 1.13 (3H, s, (major diastereomer)); δ_C ^{13}C NMR (101 MHz, $CDCl_3$) 98.7, 74.7, 71.7, 54.4, 29.5, 26.2, 24.9, 24.2, 17.8 (major epimer); 108.8, 82.5, 71.8, 56.0, 30.9, 26.2, 24.5, 24.3, 21.9 (minor epimer); GC–HRMS (EI), found 174.1252 $[M]^+$, $C_9H_{18}O_3$ requires 174.1256.

*2.2.13. Synthesis of (1S, 5S)-7,7-dimethyl-6,8-dioxa-bicyclo[3.2.1]octane (**16**).* Compound **15** (87.2 mg, 0.5 mmol) and $FeClO_4.3H_2O$ (17.8 mg, 0.1 mmol) were dissolved in dichloromethane (5 mL) and stirred at room temperature for 5 h. The solvent was removed in vacuo and the crude material was purified by column chromatography using pentane/Et_2O (9:1). The volatile contributor of beer aroma **16** was isolated in 75% isolated yield with 96% ee.[14d] The enantiomeric excess was determined by Chiral GC using a β-dex

column. $[\alpha]_D^{20}$ −91.0 (*c* 1.0, Et_2O); lit.[14d] $[\alpha]_D^{20}$ −92.0 (*c* 2.0, Et_2O); R_f (pentane/Et_2O, 9:1)=0.75; δ_H ^{1}H NMR (400 MHz, $CDCl_3$) 5.50 (1H, s, O−C*H*−O), 3.83 (1H, d, *J* 3.7 Hz, O−C*H*−CH_2), 2.06–1.79 (2H, m), 1.74–1.49 (m, 4H), 1.42 (3H, s, −CH_3), 1.26 (3H, s, −CH_3); δ_C ^{13}C NMR (101 MHz, $CDCl_3$) 101.9, 80.4, 79.4, 30.2, 29.0, 25.0, 20.5, 15.6; GC–HRMS (EI), found 142.1994, requires $C_8H_{14}O_2$ 142.1994.

2.3. General procedure for microwave irradiation experiments

All microwave experiments were performed using the CEM Discover Synthesizer possessing a single-mode microwave cavity producing controlled irradiation at 2.45 GHz. Experiments were carried out in standard microwave process Pyrex vials (capacity 10 mL) using the high absorbance level. Reaction temperature was measured by IR probe built in a microwave. Reaction time reflects irradiation times at fixed hold time.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.05.032.

References and notes

1. Kinzer, G. W.; Fentiman, A. F.; Page, T. F.; Foltz, R. L.; Vite, J. P.; Pitman, G. B. *Nature (London)* **1969**, *221*, 477.
2. Wood, D. L.; Browne, L. E.; Ewing, B.; Lindahl, K.; Bedard, W. D.; Tilden, P. E.; Mori, K.; Pitman, G. B.; Hughes, P. R. *Science* **1976**, *192*, 896.
3. Francke, W.; Schröder, F.; Philipp, P.; Meyer, H.; Sinnwell, V.; Gries, G. *Bioorg. Med. Chem.* **1996**, *4*, 363.
4. Singh, S.; Duffy, C. D.; Shah, S. T. A.; Guiry, P. J. *J. Org. Chem.* **2008**, *73*, 6429.
5. Singh, S.; Guiry, P. J. *Eur. J. Org. Chem.* **2009**, 1896.
6. Singh, S.; Guiry, P. J. *J. Org. Chem.* **2009**, *74*, 5758.
7. Selected references for the asymmetric synthesis of frontalin, see: (a) Hicks, D. R.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1976**, 869; (b) Magnus, P.; Roy, G. *J. Chem. Soc., Chem. Commun.* **1978**, 297; (c) Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1984**, 578; (d) Hosokawa, T.; Makabe, Y.; Shinohara, T.; Murahashi, S.-I. *Chem. Lett.* **1985**, 1529; (e) Whitesell, J. K.; Buchanan, C. M. *J. Org. Chem.* **1986**, *51*, 5443; (f) Fujisawa, T.; Takemura, I.; Ukaji, Y. *Tetrahedron Lett.* **1990**, *31*, 5479; (g) Mash, E. A.; Fryling, J. A. *J. Org. Chem.* **1991**, *56*, 1094; (h) Nemoto, H.; Yamada, T.; Ishibashi, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3149; (i) Davis, F. A.; Reddy, G. V.; Chen, B.-C.; Kumar, A.; Haque, M. S. *J. Org. Chem.* **1995**, *60*, 6148; (j) Nishimura, Y.; Mori, K. *Eur. J. Org. Chem.* **1998**, 233; (k) Maezaki, N.; Shogaki, T.; Uchida, M.; Tokuno, K.; Imamura, T.; Tanaka, T.; Iwata, C. *Chem. Pharm. Bull.* **1998**, *46*, 217; (l) Kouklovsky, C.; Dirat, O.; Berranger, T.; Langlois, Y.; Tran-Huu-Dau, M. E.; Riche, C. *J. Org. Chem.* **1998**, *63*, 5123; (m) Majewski, M.; Nowak, P. *Tetrahedron: Asymmetry* **1998**, *9*, 2611; (n) Bravo, P.; Frigerio, M.; Ono, T.; Panzeri, W.; Peseti, C.; Sekine, A.; Viani, F. *Eur. J. Org. Chem.* **2000**, 1387; (o) Ambrosi, P.; Arnone, A.; Bravo, P.; Bruché, L.; De Cristofaro, A.; Francardi, V.; Frigerio, M.; Gatti, E.; Germinara, G. S.; Panzeri, W.; Pennacchio, F.; Pesenti, C.; Rotundo, G.; Roversi, P. F.; Salvadori, C.; Viani, F.; Zanda, M. *J. Org. Chem.* **2001**, *66*, 8336; (p) Jew, S.-S.; Lim, D.-Y.; Kim, J.-Y.; Kim, S.-J.; Roh, E.-Y.; Yi, H.-J.; Mo, J.-M.; Park, B.-S.; Jeong, B.-S.; Park, H.-G. *Tetrahedron: Asymmetry* **2002**, *13*, 155; (q) Trzoss, M.; Shao, J.; Bienz, S. *Tetrahedron* **2002**, *58*, 5885; (r) Chenevert, R.; Caron, D. *Tetrahedron: Asymmetry* **2002**, *13*, 339; (s) Yus, M.; Ramón, D. J.; Prieto, O. *Eur. J. Org. Chem.* **2003**, 2745; (t) Yang, X.; Luo, S.; Hua, C.; Zhai, H. *Tetrahedron* **2003**, *59*, 8551; (u) Prasad, K. R.; Chandrakumar, A.; Anbarasan, P. *Tetrahedron: Asymmetry* **2006**, *17*, 1979; (v) Ortiz, B.; Sanchez-Obregon, R.; Toscano, R. A.; Yuste, F. *Synthesis* **2008**, 2105.
8. Optical rotation of (−)-frontalin $[\alpha]_D^{20}$ −53.6 (*c* 1.44, 89.9% ee, Et_2O) [lit.[7h] $[\alpha]_D^{19}$ −53.7 (*c* 0.67, Et_2O), lit.[7j] $[\alpha]_D^{24}$ −50.3 (*c* 1.63, 89.1% ee, Et_2O) and lit.[7t] $[\alpha]_D$ −51.6 (*c* 0.5, 85% ee, Et_2O)]; (+)-frontalin $[\alpha]_D^{20}$ +52.3 (*c* 1.05, 92.8% ee, Et_2O) [lit.[7e] $[\alpha]_D$ +54.3 (*c* 0.3, Et_2O), lit.[7c] $[\alpha]_D^{21}$ +52.4 (*c* 4.0, Et_2O)]; (−)-*exo*-isobrevicomin $[\alpha]_D^{20}$ −56.4 (*c* 1.13, 97.9% ee, Et_2O) [lit.[9b] $[\alpha]_D^{22}$ −60.4 (*c* 1.16, $CHCl_3$), lit.[9c] $[\alpha]_D^{28}$ −55.9 (*c* 1.00, $CHCl_3$)].
9. (a) Prasad, K. R.; Anbarasan, P. *Tetrahedron: Asymmetry* **2007**, *18*, 1419; (b) Mori, K.; Takikawa, H.; Nishimura, Y.; Horikiri, H. *Liebigs Ann./Recl.* **1997**, 327; (c) Taniguchi, T.; Takeuchi, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1998**, *9*, 1451; (d) Mori, K. *Chem. Commun.* **1997**, 1153; (e) Bouziane, A.; Regnier, T.; Carreaux, F.; Carboni, B.; Bruneau, C.; Renaud, J.-L. *Synlett* **2010**, 207.
10. (a) Chandrasekhar, S.; Reddy, C. R. *Tetrahedron: Asymmetry* **2002**, *13*, 261; (b) Albert, B. J.; Sivaramakrishnan, A.; Naka, T.; Czaicki, N. L.; Koide, K. *J. Am. Chem. Soc.* **2007**, *129*, 2648.
11. The enantiomeric excess of (−)-*exo*-isobrevicomin **3** was determined by GC and to confirm the retention time its enantiomer was synthesized. The synthetic details for the synthesis of both enantiomers and the chromatograms are given in the Supplementary data.
12. Tressl, R.; Friese, L.; Fendesack, F.; Köppler, H. *J. Agric. Food Chem.* **1978**, *26*, 1422.
13. Naya, Y.; Kotake, M. *Tetrahedron Lett.* **1967**, *26*, 2459.
14. (a) Masaki, Y.; Nagata, K.; Serizawa, Y.; Kaji, K. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1983**, *26*, 545; (b) *Chem. Abstr.* **1983**, *101*, 23162x; (c) Ibrahim, N.; Eggimann, T.; Dixon, E. A.; Wieser, H. *Tetrahedron* **1990**, *46*, 1503; (d) Curran, D. P.; Heffner, T. A. *J. Org. Chem.* **1990**, *55*, 4585; (e) Crispino, G. A.; Sharpless, K. B. *Synlett* **1993**, 47; (f) Steinreiber, A.; Mayer, S. F.; Faber, K. *Synthesis* **2001**, 2035.
15. Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.
16. Kim, G.-J.; Lee, H.; Kim, S.-J. *Tetrahedron Lett.* **2003**, *44*, 5005.